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- a. providing a mouse embryonic stem cell comprising a disrupted endogenous serine protease gene;
  - b. introducing the mouse embryonic stem cell into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and
  - c. breeding the chimeric mouse to produce the transgenic mouse,
- wherein the transgenic mouse whose genome comprises a heterozygous disruption in the endogenous serine protease gene produces a transgenic mouse having a homozygous disruption in an endogenous serine protease gene and exhibiting a developmental abnormality during embryonic development.
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**In the Drawings:**

Please replace originally filed Figure 2B with new Figure 2B attached herewith.

**REMARKS**

**I. Amendments**

The amendments to the specification were made in order to overcome typographical or grammatical objections. Appendix A, attached herewith, contains a marked-up version of the changes made to the specification by this amendment.

In the claims, claims 1-16 are canceled, and new claims 17-20 are added. The newly added claims do not add new matter and are completely supported throughout the application as originally filed. More particularly, newly added claims 17-20, drawn to a transgenic mouse comprising a homozygous disruption in an endogenous sulfotransferase gene, a method of producing said mouse, and cells or tissue isolated from said mouse can be found, for example, at page 11, line 18 through page 16, line 2, and at page 51, line 22 through page 52, line 2, of the specification.

The drawings are amended to submit new Figure 2B in response to informalities objected to by the Draftsperson on Form PTO-948. In particular, newly submitted Figure 2B is intended to correct errors in margins, views and number and letter format, which were noted by the Draftsperson. Further, the newly submitted Figure 2B incorporates corrections to mislabeled nucleotide sequence identifiers for SEQ ID NO:3 and SEQ ID NO:4, which originally were

originally mislabeled as SEQ ID NO:2 and SEQ ID NO:3, respectively. The amendment to the drawings is supported by the application as originally filed. More specifically, support for the amendment to Figure 2B can be found at page 8 of the specification, namely in the Brief Description of the Drawings, where the sequences were correctly identified. The newly submitted drawings do not add new matter and are believed to be in compliance with the requirements for drawings under 37 CFR 1.84. A version of Figure 2B with the proposed changes to the sequence identifiers is enclosed herewith, along with a clean version of new Figure 2B with the corrected errors and proposed changes to the sequence identifiers.

The foregoing amendments are made solely to expedite prosecution of the application and are not intended to limit the scope of the invention. Further, the amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in a related application. The Applicants reserve the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation, or continuation-in-part application.

Upon entry of the amendment, claims 17-20 are pending in the instant application.

## **II. Rejections**

### ***A. Rejection under 35 U.S.C. § 112, first paragraph***

Claims 1-16 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the relevant art at the time the application was filed, had possession of the claimed invention. Applicants disagree with the Examiner's assertions and respectfully traverse this rejection. However, as a result of the cancellation of these claims, the Examiner's rejection under 35 U.S.C. § 112, first paragraph, is no longer relevant.

Claims 8 and 9 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the relevant art at the time the application was filed, had possession of the claimed invention. Applicants disagree with the Examiner's assertions and respectfully traverse this rejection. However, as a result of the cancellation of these claims, the Examiner's rejection under 35 U.S.C. § 112, first paragraph, is no longer relevant.

Claim 16 was rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art at the time the application was filed, had possession of the claimed invention. Applicants disagree with the Examiner's assertions and respectfully traverse this rejection. However, as a result of the cancellation of these claims, the Examiner's rejection under 35 U.S.C. § 112, first paragraph, is no longer relevant.

Claims 1-16 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Applicants disagree with the Examiner's assertions and respectfully traverse this rejection. However, as a result of the cancellation of these claims, the Examiner's rejection under 35 U.S.C. § 112, first paragraph, is no longer relevant.

Applicants submit that new claims 17-20 are fully described and enabled by the teachings of the application under 35 U.S.C. § 112, first paragraph. As claims 1-16 are no longer relevant as a result of the cancellation of these claims, and new claims 17-20 are fully described and enabled by the application under 35 U.S.C. § 112, first paragraph, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

***B. Rejection under 35 U.S.C. § 112, second paragraph***

Claims 5-9 and 11-16 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. Applicants disagree with the Examiner's assertions and respectfully traverse the rejections under 35 U.S.C. § 112, second paragraph. However, in view of the cancellation of claims 5-9 and 11-16, the rejection is moot. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

The Applicants submit that new claims 17-20 are definite and particularly point out and distinctly claim the subject matter regarded as the invention in accordance with 35 U.S.C. § 112, second paragraph.

It is believed that the claims are currently in condition for allowance, and notice to that effect is respectfully requested. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-1271 under Order No. R-386.

Respectfully submitted,

Date: 11/20/2002

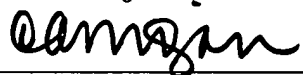
  
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**CERTIFICATE OF MAILING UNDER 37 CFR 1.8**

I hereby certify that this correspondence and its listed enclosures is being deposited with the United States Postal Service as First Class Mail, postage paid, in an envelope addressed to: Assistant Commissioner for Patents and Trademarks, Washington, D.C. 20231, Box NF  
Amendment on **November 20, 2002**

Name: **Deborah A. Mojarro**

Signed: 

Date: 11/20/02

## Appendix A

### Paragraph beginning at page 57, line 5:

The present invention relates to transgenic animals, as well as compositions and methods relating to the characterization of gene function. Specifically, the present invention provides transgenic mice comprising mutations in a serine protease gene. ~~The Such~~ transgenic mice are useful as models for disease and for identifying agents that modulate gene expression and gene function, and as potential treatments for various disease states and disease conditions.

### Paragraph beginning at page 7, line 1:

The term "target gene" (alternatively referred to as "target gene sequence" or "target DNA sequence" or "target sequence") refers to any nucleic acid molecule or polynucleotide of any gene to be modified by homologous recombination. The target sequence includes an intact gene, an exon or intron, a regulatory sequence or any region between genes. The target gene comprises a portion of a particular gene or genetic locus in the individual's genomic DNA. As provided herein, the target gene of the present invention is a serine protease gene. A "serine protease gene" refers to a sequence comprising SEQ ID NO:1 or comprising the sequence encoding the serine protease gene identified in ~~Genebank~~GenBank as Accession No. AF042822; GI:7330637. In one aspect, the coding sequence of the "serine protease gene" comprises SEQ ID NO:1 or comprises the gene identified in ~~Genebank~~GenBank as Accession No. AF042822; GI:7330637.